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OIPE JC106 JUN 0 1 2004 PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Laurent LECOURT et al.

Serial No. 09 / 920,806

Filed August 3, 2001

Conf. 7152

Group 3761

Examiner M. Mendoza

Inhalable aerosol medicament for the treatment or prevention of pain

DECLARATION UNDER RULE 132

Assistant Commissionner for Patents
P.O. Box 1450
Alexandria,Virginia 22313-1450

Sir :

I, Laurent LECOURT, a citizen of France, residing at: 2 route des Postillons, Dept. 92, SEVRES, France, declare that:

I am currently employed by AIR LIQUIDE SANTE (INTERNATIONAL) 10 rue Cognacq - Jay 75341 PARIS, France.

I graduated as a pharmacist from the University of Toulouse, France.

I have over 10 years experience in the medical field, and especially in oncology, resuscitation and pneumology.

I work in medical gases department and I'm in charge of the development and research of new medical gases or new medical application for gases.

I am named inventor or co-inventor in several US and European patents or pending patent applications in this field.

I make this declaration in support of the present application, and to provide evidence and rebuttal to the issues raised in the Official Action of October 29, 2003.

L.L.

Indeed, I consider that Keller et al (US'591) in view of publication RD 17066, one of the publications cited by Keller et al, does not disclose or suggest the claimed invention for the following reasons.

When reading Keller et al's document, it appears that only fluorinated alkanes mixed with CO_2 (i.e. carbon dioxide) are considered as improving the properties of aerosols containing pharmaceutically active compounds (see the abstract of Keller et al). In fact, Keller et al are completely silent about N_2O.

Indeed, Keller et al advocate a mixture of alkanes + CO_2, but not N_2O as propellant gas.

As to the RD 17066 publication, the RD 17066 publication RD 17066 is completely silent about the use of N_2O in combination with one or several of the specific compounds listed in the claimed invention.

According to the present invention, the combination of N_2O gas and one or several of the specific compounds recited in the claims leads to a synergistic and improved effect in terms of pain treatment.

Indeed, N_2O molecules have an antagonist effect of NMDA receptors that are involved in the pain mechanism, i.e. these N_2O molecules are going to block the NMDA receptors in brain thereby avoiding any addiction of the patient to the active compound that he takes for diminishing his pain, such as morphine or opium-containing substances.

The synergistic effect of such a combination N2O+specific compounds is demonstrated by the comparative test results set forth in the slides enclosed with this declaration. The slides are numbered 1 to 13.

These test results have already been produced to the European Patent Office in support of the EPO equivalent of the present application and have been considered convincing by the EPO Examiner, which immediately granted the corresponding EPO patent n° EP1177793 B1.

As you will see on SLIDES 1 to 13, comparative tests have been made with 2 groups of animals (i.e. mice):

- Group 1: "non-painful" animals
- Group 2: "painful" animals

SLIDE n° 1 shows the therapeutic scheme that has been followed and allows one to better understand the results.

Generally speaking, in a mammal, pain modulation results from a balance between the activity of the antinociceptive and pronociceptive systems.
"SLIDE n°1" shows that opiate compounds are able to activate the following:

1) Systems that inhibit nociception (i.e. analgesia). The left part of the scheme corresponds to a short-term effect that it classical of analgesia; and

2) Systems that facilitate nociception (i.e. hyperalgia), surprisingly so, through the activation of NMDA receptors (N methyl D Aspartate).

LC

The analgesic effect due to the administration of an opiate substance would then be the result of the functioning of the two systems.

The activation of the systems that facilitate nociception (pronociceptive systems) could lead to a partial or total masking of analgesia, corresponding to the phenomenon of tolerance or addiction to morphine-substances, which explains also the necessity, for obtaining a same antalgic effect (i.e. a diminution of the pain), to increase the quantity of morphine-compound administrated to the patient.

Such a tolerance or addiction is not the result of a real decrease of efficiency of the opiate analgesia, but rather to a pain hyper-sensibility (nociceptive system activated).

Hence, blocking the NMDA receptors leads also to a simultaneous blocking of the systems that facilitate nociception and an increase of the pain-resistance of the patient, which is beneficial for him as he will suffer less.

In contrast, an administration of analgesic products/compounds over a long period of time involves a kind of addiction and hence a decrease of the pain-resistance of the patient, which is not beneficial for him as he will suffer more.

In other words, albeit the advantages of opiate analgesia during an surgical operation, it has been demonstrated that an acute or chronic administration of a opiate or morphine-compound or similar can surprisingly lead to an hypersensitivity of the patient with respect to "long-duration" pain in a "normal" mammal, the duration of said hypersensitivity being proportional to the dosage of the morphine-product administrated.

Said hypersensitivity could explain long-duration hyperalgesia and/or post-operation recurrent pain affecting some patients.

The goal of the present invention combining N_2O with a morphine-compound or similar (as recited in the claimed invention) is to allow a potentialisation effect of the antalgic effect and to stop the hyperalgesic effect of the morphine-compound or similar in terms of duration and amplitude.

As shown on the left part of SLIDE 1, the tests have demonstrated that N_2O molecule is able to block the NMDA receptors thereby leading to an increase to the pain tolerance for the patient and also thereby avoiding or minimizing the so-called long-term pain hypersensitivity effect.

That is to say that the present invention is based on a synergistic effect of N_2O with one or several of the recited pain-treating compounds.

TEST N°1: See "SLIDES" n° 2 and 3

Fentanyl (opiate-morphine compound) has been administrated by inhalation to "normal" mice, at a dose of 4 x 60 µg/kg. The gas used was either air or N_2O (in dilution with O_2).

After that, mechanical pressures (from 200 g to 600 g) have been applied on the mice legs in order to determinate the "pain-tolerance threshold" (called hereafter "PTT"). The mice usually start to scream with

LL

the apparition of pain. This is called the test of *Randall-Selitto*. The basic level (i.e. pain-tolerance threshold PTT) is of about 300 g of pressure.

As represented on SLIDE n°3, the administration of fentanyl (a morphine compound) leads, in a first time, to an antalgic effect (as the PTT raises to 600 g), but on can see that it does not last for a long time, i.e. only a few hours.
Mice that have been pre-treated with N_2O return to their PTT of 300 g, whereas with non-treated mice, the PTT falls down to only about 200 g, which phenomenon lasts several days.

This experience shows clearly that N_2O totally blocks the hyperalgesia phenomenon linked to morphine-compounds.

It is understandable that the N_2O non-treated mice should take a greater dosage of antalgic drug for decreasing their pain, in the case they would be submitted to nocicpetive stimulation (i.e. mechanical pressure on their legs).

TESTS N°2 & 3: See "SLIDES" n° 4 & 5 and n° 6 & 7, respectively

Test n°2 is similar to test n°1, except that, for comparative reasons, the fentanyl compound has been replaced by a placebo (i.e. a non-active substance), such as NaCl.

The experience shows that it is well the fentanyl compound that has an hyperalgic action on the brain (SLIDES" n° 4 & 5).

Indeed, NaCl does not lead to any modification of the PTT (no analgesic effect) and to any "delayed" effect.

Further, test n°2 shows also that, even with a low dose of fentanyl, the hyperalgic effect is still present, even if reduced in comparison with the one obtained with higher doses.

Besides, test n°3, represented on "SLIDES" 6 & 7, is similar to test n°2 except that it has been conducted with an elevated dosage of fentanyl (i.e. 4 x 100 µg/kg). This test n°3 shows that morphine leads to a long-term effect of 1 week.

In conclusion, the more the fentanyl dosage, the more the delayed effect and the more the efficiency of the N_2O gas protection on the NMDA receptors.

TEST N°4: See "SLIDES" n° 8 & 9

Naloxone has also been administrated to the mice during test n° 1 to 3, in order to confirm the action on opioide receptors.

Indeed, naloxone is an antagonist of µ receptors (but naloxone has no own antalgic effect) and acts in blocking the left part of the fentanyl action mechanism as represented on SLIDE n°1 and, in the same time, in activating the right part by means of the NMDA receptors, which will lead to an hyperalgesia (i.e. a decreasing of the PTT).

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The test n°4 shows that mice pre-treated with N_2O do not react after the administration of naloxone, due to the fact that N_2O acts on NMDA receptors.

TESTS N°5 & 6: See "SLIDES" n° 10 to 12

The experimental protocol of test n°1 has been repeated on mice pre-treated by an injection of carragenine (which is an inflammatory product) thereby causing an inflammation of the left rear legs of the mice (this group of mice is called "painful animals").

Such a model reproduces the component of a post-operation pain.

It has been observed that, with "painful mice", a synergistic effect is exhibited when N_2O is administrated in association with fentanyl (J0 = day 0), in which the synergistic effect combines with the hyperalgesia preventing effect as explained above.

After 1 day (J1), a second administration (by inhalation) of an opiate compound (morphine) is done. Afterwards, a more important/efficient response (i.e. antalgic effect) is observed in the group of mice that have inhaled the opiate compound in combination with N_2O as the PTT is of between 500 and 600 g (brown curve on the figure).

In contrast, in the group of mice that is not been ventilated with N_2O, the PTT falls down to only 400 g, which means that a same dose of opiate compound has clearly a lower effect.

This shows that N_2O allows to avoid increasing, day after day, the dose/quantity of morphine products administrated the patients and thereby to limit the secondary effects of these products on the thus treated patients (such as respiratory distress, etc...), which means that N_2O allows to improve the quality of life of the patients treated with morphine or similar "anti-pain" compounds.

GENERAL CONCLUSION: "SLIDE n° 13"

These tests demonstrate that N_2O can block NMDA receptors thereby, when administrated concurrently with an active product (morphine or similar), improving the PTT while avoiding the hypersensibilsation effect that takes place when air is used in lieu of N_2O.

In other words, the combined administration of N_2O and with one of the recited components leads to a synergistic effect that was not obvious to one skilled in the art at the time the application was filed.

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Thus, I declare that the combination of Keller et al in view of publication RD 17066 does not disclose or suggest the claimed invention.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of United States Code and that such wilful false statements may jeopardize the validity of the application or any patent issuing thereon.

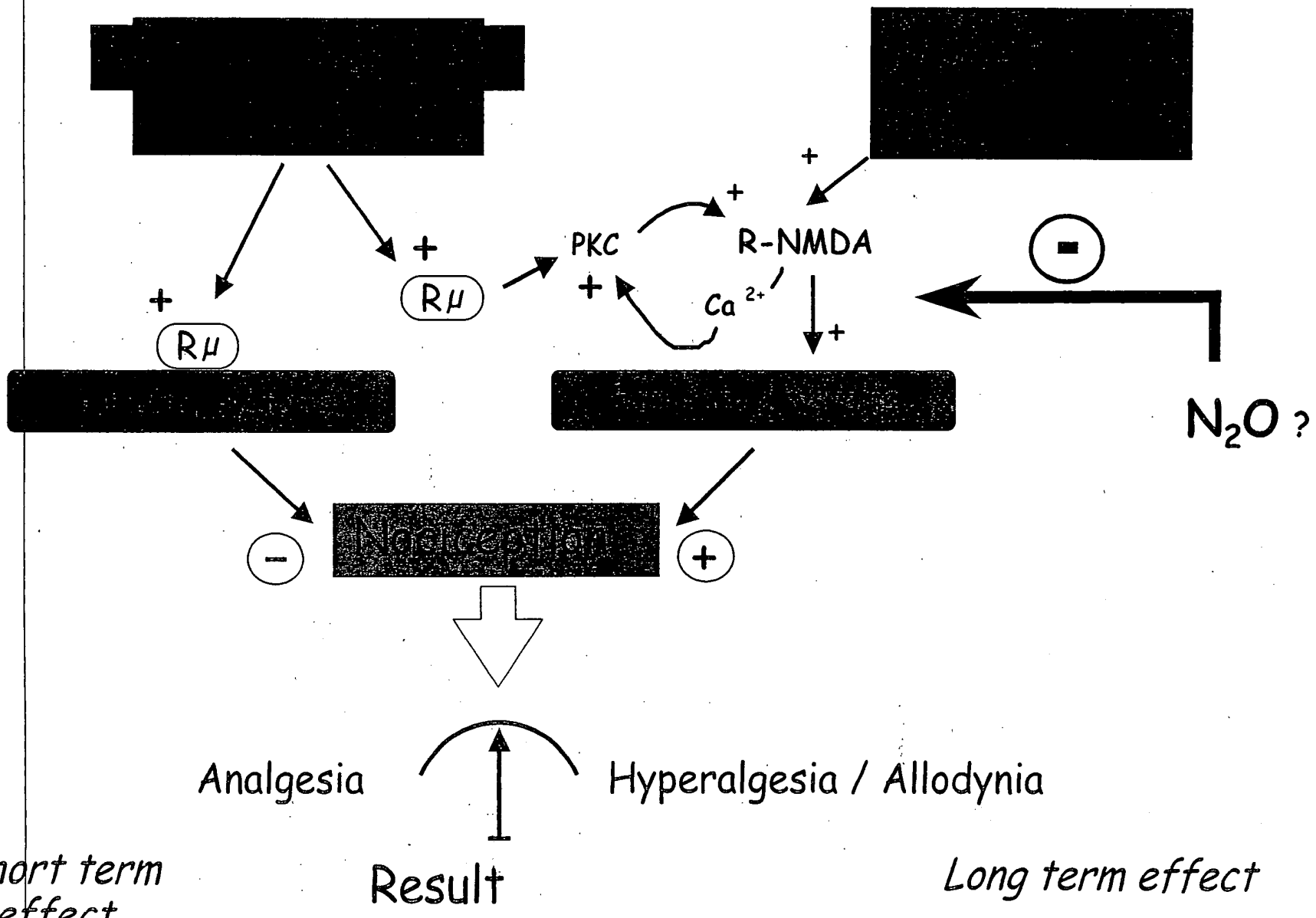
LAURENT LECOURT

February 24, 2004

DATE

OIPE JC106 JUN 01 2004 PATENT & TRADEMARK OFFICE

Therapeutical scheme

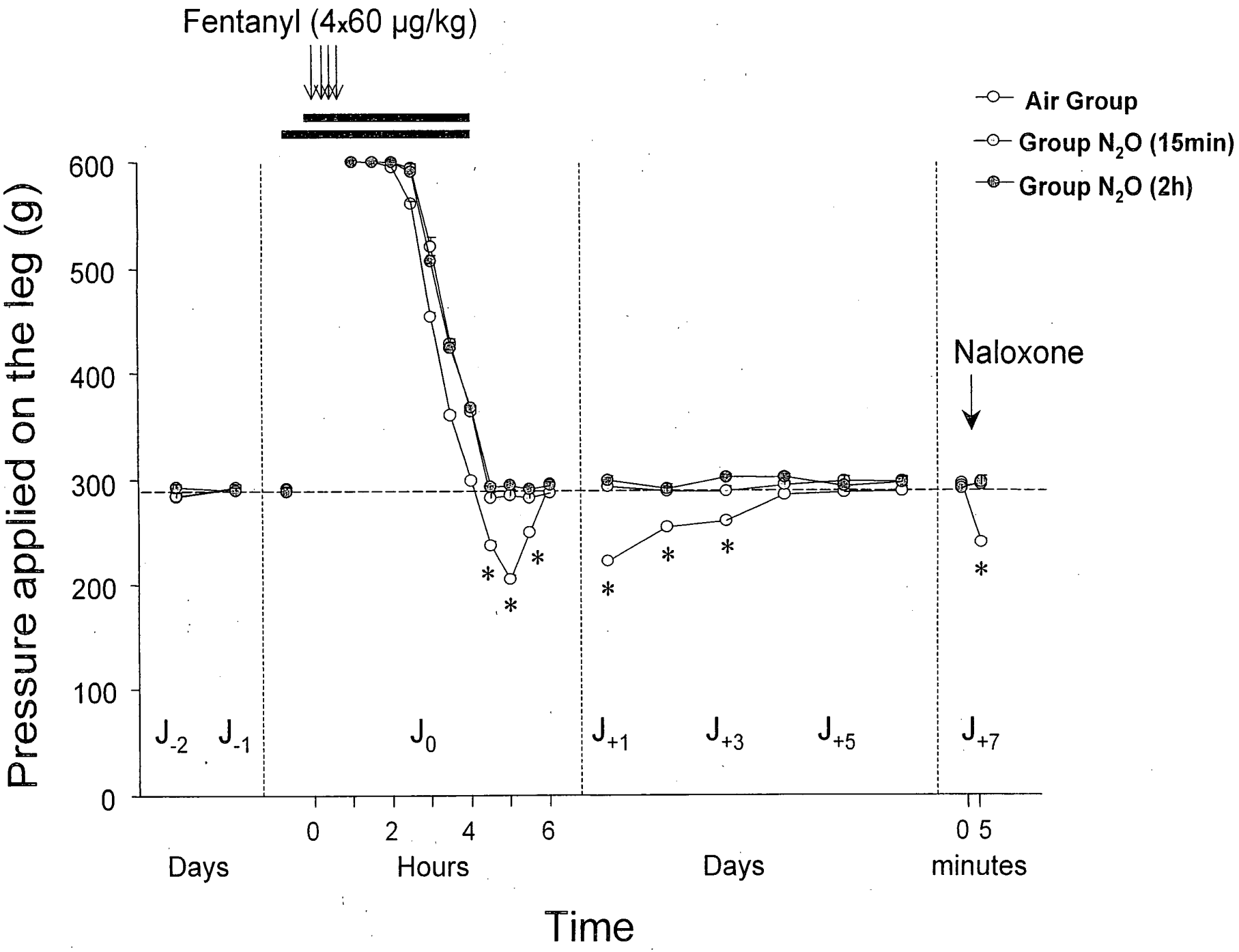


Test 1 : 4x60µg/kg of fentanyl

➲ administration of medical air during the duration of the test,

➲ administration of N_2O/O_2 (50%/50%) 15 minutes before the 1st injection of fentanyl and during all the analgesic effect, then medical air,

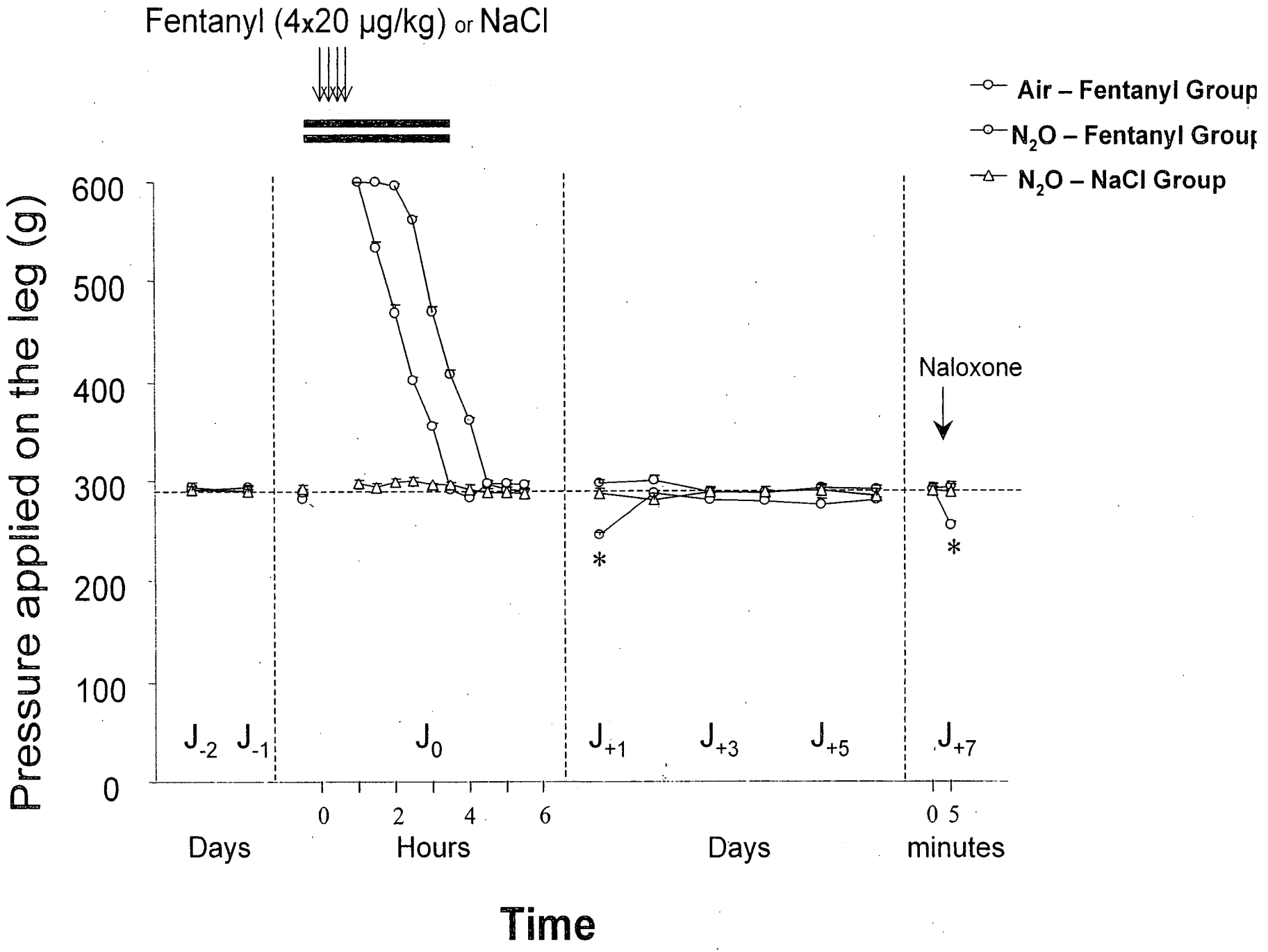
➲ N_2O/O_2 (50%/50%) 2 hours before the 1st injection of fentanyl and during all the analgesic effect, then medical air.


Fentanyl (4x60 µg/kg)
Air Group
Group N2O (15min)
Group N2O (2h)
Naloxone
Pressure applied on the leg (g)
600
500
400
300
200
100
0
J-2
J-1
J0
J+1
J+3
J+5
J+7
0
2
4
6
0 5
Days
Hours
Days
minutes
Time

Test 2 : 4x20µg/kg of fentanyl or NaCl

- ➲ medical air + injection of fentanyl,
- ➲ N_2O/O_2 (50/50) + injection of fentanyl,
- ➲ N_2O/O_2 (50/50) + injection of NaCl.

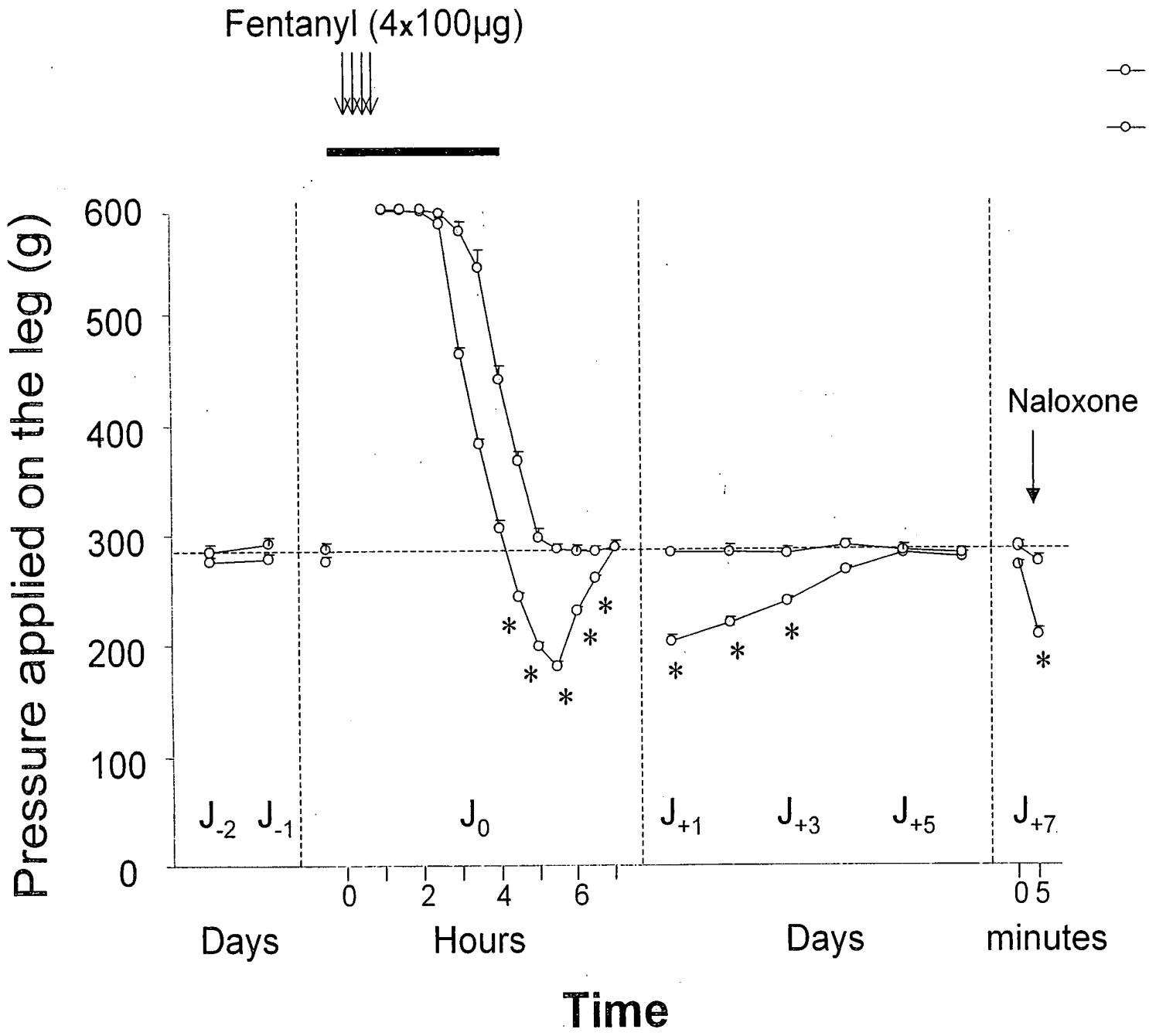
NB : the gaseous mixture is given 30 minutes before the first injection of fentanyl (or NaCl) and during all the analgesic effect ; then it is replaced by medical air.


Fentanyl (4x20 µg/kg) or NaCl
Air – Fentanyl Group
N2O – Fentanyl Group
N2O – NaCl Group
Pressure applied on the leg (g)
600
500
400
300
200
100
0
Naloxone
J-2
J-1
J0
J+1
J+3
J+5
J+7
0
2
4
6
0 5
Days
Hours
Days
minutes
Time

Test 3 : 4x100µg/kg of fentanyl

- under medical air + injection of fentanyl,
- under N_2O/O_2 (50/50) + injection of fentanyl.

NB : The gaseous mixture is given 30 minutes before the first injection of fentanyl and during all the analgesic effect ; then it is replaced by medical air.

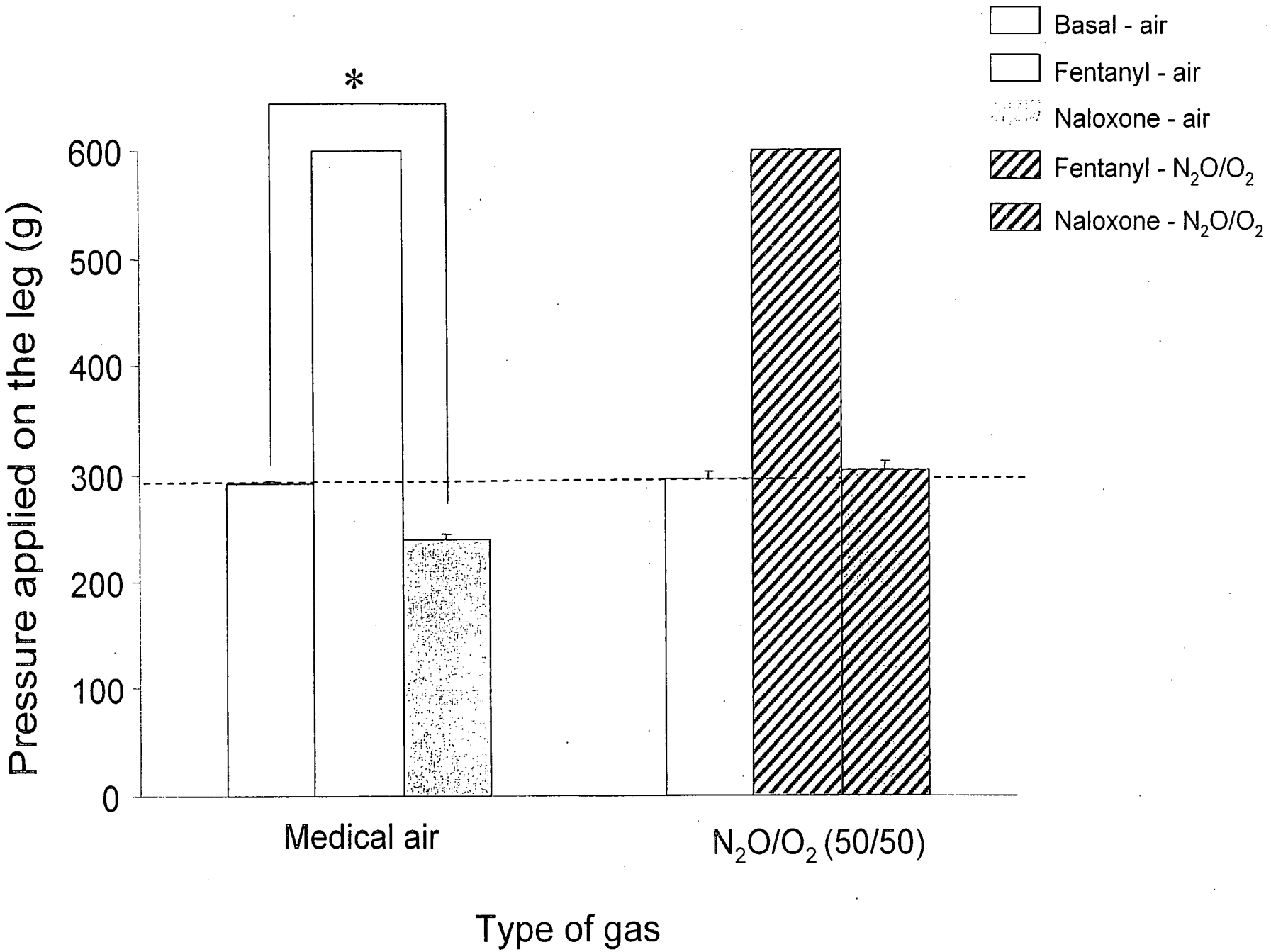

Fentanyl (4x100µg)
Air Group
N2O Group
Pressure applied on the leg (g)
600
500
400
300
200
100
0
Naloxone
J-2
J-1
J0
J+1
J+3
J+5
J+7
0
2
4
6
0 5
Days
Hours
Days
minutes
Time

Test 4

Effect of the administration of naloxone (1mg/kg; s.c.), during the analgesic effect of fentanyl (4x60µg/kg),

- medical air + fentanyl+ Naloxone,
- N_2O/O_2 (50/50) + fentanyl+ Naloxone.

NB:The gaseous mixture is given 30 minutes before the first injection of fentanyl and during all the analgesic effect; then it is replaced by medical air.


Basal - air
Fentanyl - air
Naloxone - air
Fentanyl - N2O/O2
Naloxone - N2O/O2
*
600
500
400
300
200
100
0
Pressure applied on the leg (g)
Medical air
N2O/O2 (50/50)
Type of gas

Painful Animals

(inflammatory model with carragenine)

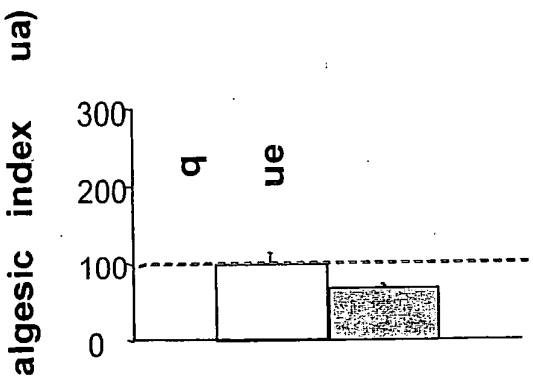
Test 5 : 4x60µg/kg of fentanyl

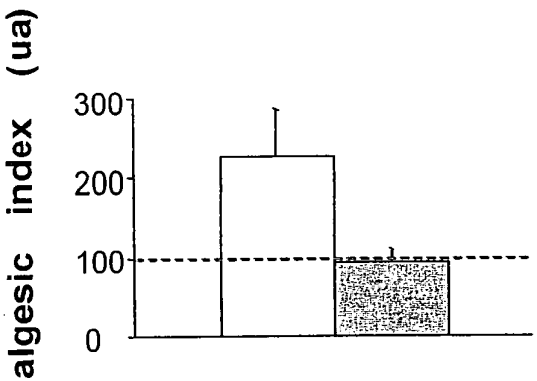
Results of the ipsilateral foot to injection of carragenine

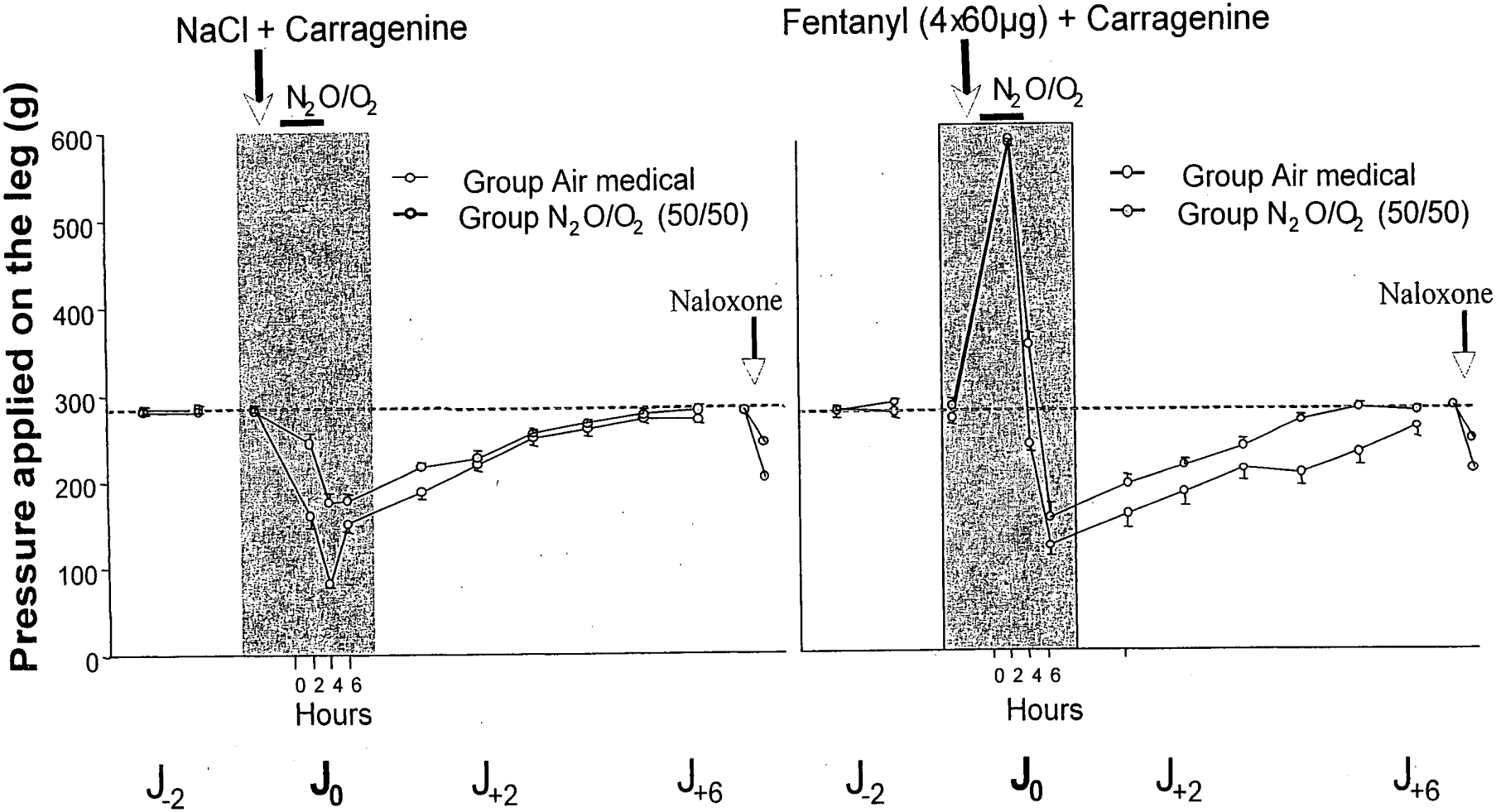
All animals receive an intraplantar injection of carragenine (0.2 ml d of solution to 1p100 of carragenine in physiological salt solution) in the left hind foot.

- under medical air with or without fentanyl ,
- under N_2O/O_2 (50%/50%) with or without fentanyl.

NB : the gaseous mixture is given 30 minutes before the first of the 4 injections of fentanyl (or physiological salt solution) followed 5 minutes later by carragenine.


algesic index ua)
300
200
100
0
q
ue


algesic index (ua)
300
200
100
0

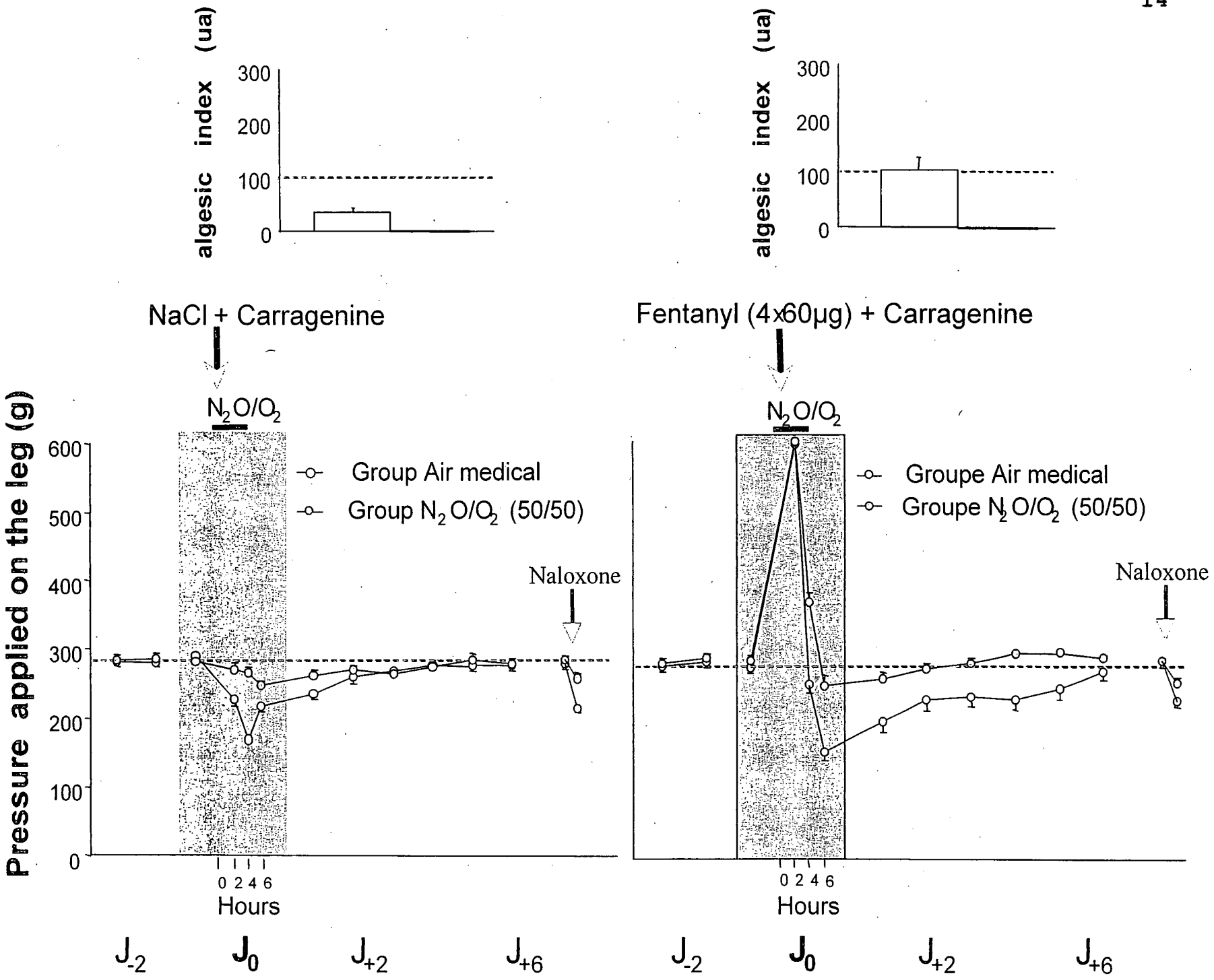

NaCl + Carragenine
N2O/O2
Fentanyl (4x60µg) + Carragenine
N2O/O2
Pressure applied on the leg (g)
600
500
400
300
200
100
0
Group Air medical
Group N2O/O2 (50/50)
Naloxone
0 2 4 6
Hours
J-2
J0
J+2
J+6

Test 6 : 4x60µg/kg of fentanyl

Results of the controlateral foot to the carragenine injection All animals receive an intraplantar injection of carragenine (0.2 ml of a solution to 1p100 of carragenine in physiological salt solution) in the left hind foot.

- under medical air with or without fentanyl ,
- under N_2O/O_2 (50/50) with or without fentanyl.

NB : the gaseous mixture is given 30 minutes before the first of the 4 injections of fentanyl (or physiological salt solution) followed 5 minutes later by carragenine.

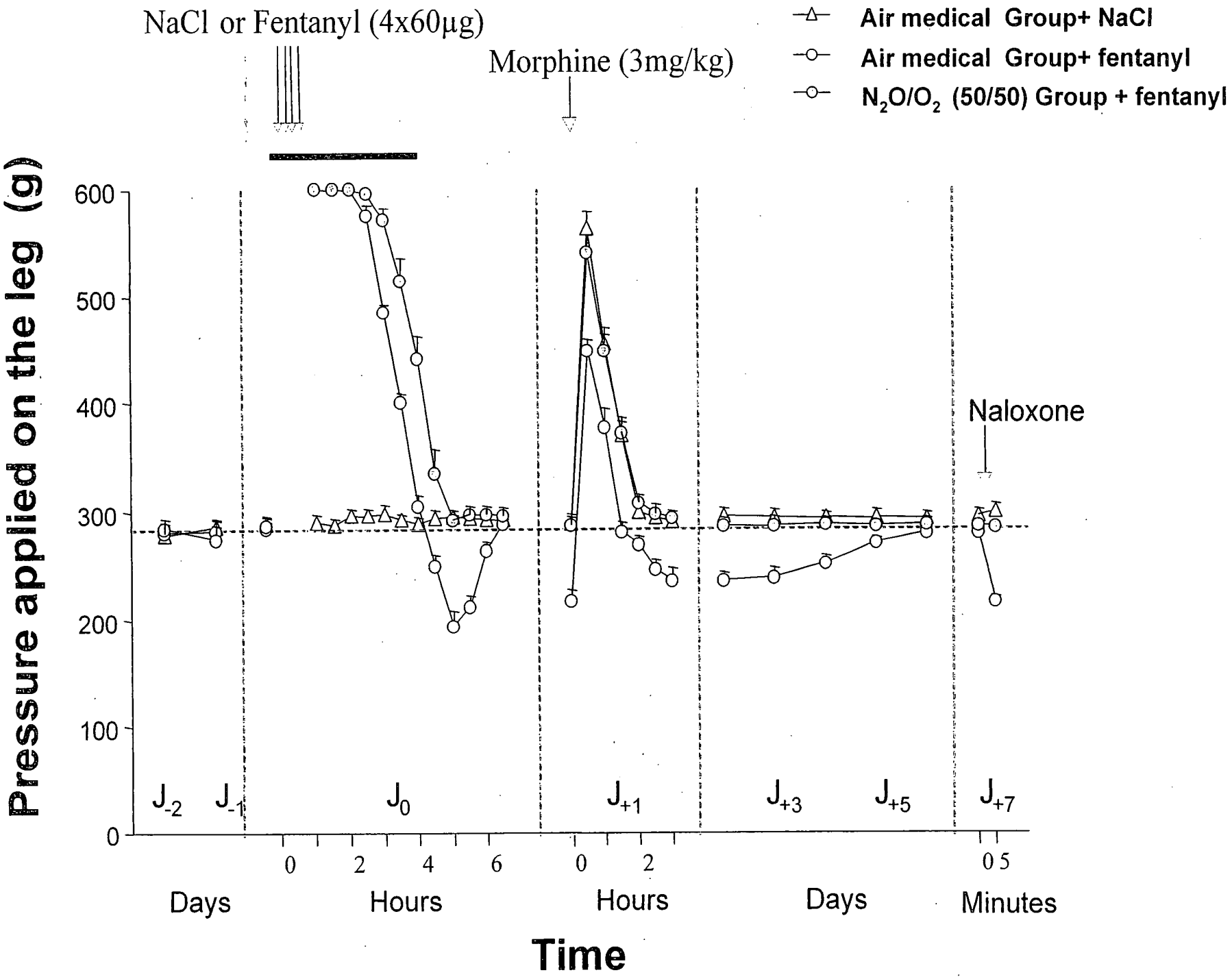

algesic index (ua)
300
200
100
0
NaCl + Carragenine
Fentanyl (4x60µg) + Carragenine
N2O/O2
Pressure applied on the leg (g)
600
500
400
300
200
100
0
Group Air medical
Group N2O/O2 (50/50)
Groupe Air medical
Groupe N2O/O2 (50/50)
Naloxone
0 2 4 6
Hours
J-2
J0
J+2
J+6

Test 7 : 4x60µg/kg of fentanyl

Comparative evaluation of effect of the morphine analgesic (3mg/Kg, s.c.) given 24 hours after fentanyl (or physiological salt solution)

- under medical air with or without fentanyl,
- under N_2O/O_2 (50%/50%) with fentanyl.

NB : the gaseous mixture is given 30 minutes before the first of the 4 injections of fentanyl (or physiological salt solution) followed 5 minutes later by carragenine.


NaCl or Fentanyl (4x60µg)
Morphine (3mg/kg)
Air medical Group+ NaCl
Air medical Group+ fentanyl
N2O/O2 (50/50) Group + fentanyl
Pressure applied on the leg (g)
600
500
400
300
200
100
0
Naloxone
J-2
J-1
J0
J+1
J+3
J+5
J+7
0
2
4
6
0
2
0 5
Days
Hours
Hours
Days
Minutes
Time

CONCLUSIONS

The gaseous mixture N_2O/O_2 (50%/50%):

➔ do not show any suitable effect on the nociceptive threshold for the normal animals but show a moderated analgesic effect for the painful animals (inflammation).

➔ produces a benefic effect by:

- potentialisating the analgesic effect of fentanyl as well as normal animals than painful one

- preventing hypersensitivity to pain involved by fentanyl as well as among normal animals than painful one (prevention of the central sensitization process as described by the effect on the controlateral foot to inflammation)

- preventing the phenomenon of tolerance to morphine produced by initial administration of fentanyl.